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PATENT APPLICATION SERIAL #: 09/898,425

TITLE: ORAL SOLID PHARMACEUTICAL FORMULATION WITH PH-DEPENDANT MULTIPHASIC RELEASE

EXAMINER: Blessing M. Fubara

PAPER BEING TRANSMITTED:

Appeal Brief Transmittal; Appeal Brief .

TO: Examiner Blessing M. Fubara

FROM: William J. Sapone, Esq., Reg. #:32,518

NUMBER OF PAGES INCLUDING THIS PAGE: 15 .

COMMENTS:

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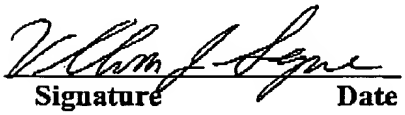

Signature Date July 11, 2005

Docket No.: 242/9-1568

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of

Applicant:	Roberto Valducci	Conf. No. 1890
Serial No.:	09/898,425	Group Art Unit: 1618
Filed :	July 3, 2001	Examiner: Blessing M Fubara
For :	ORAL SOLID PHARMACEUTICAL FORMULATION WITH PH-DEPENDANT MULTIPHASIC RELEASE	

Board of Patent Appeals and Interferences
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF TRANSMITTAL

Sir:

Enclosed is an Appeal Brief for the above-identified patent application. Please charge the Appeal Brief fee of $250.00 to deposit account no. 04-0838.

The Commissioner is authorized to charge any deficiency or credit any excess in this fee to Deposit Account No. 04-0838.

Dated: July 11, 2005

Respectfully submitted,

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APPEAL BRIEF

Sir:

This is an appeal by the Applicant from the Final Rejection dated January 11, 2005 of claims 35 and 37-46 of the above-identified application. The Notice of Appeal was filed on May 10, 2005. The appealed claims appear in Appendix A.

REAL PARTY IN INTEREST

The real party in interest is the inventor, Roberto Valducci.

RELATED PROCEEDINGS

There are no related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

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STATUS OF CLAIMS

Claims 1 through 20 were originally in this application. During prosecution, claims 1-20 were cancelled, as were later added claims 21-34. Claims 35-46 were submitted on June 3, 2003, and entered with a Request for Continued Examination filed August 4, 2003. In an amendment filed July 21, 2004, claim 36 was cancelled and claims 35, 37, and 43-46 were amended. Thus, claims 35 and 37-46 are pending, rejected, and the subject of this appeal.

STATUS OF AMENDMENTS

No amendments were made subsequent to the Final Rejection which issued on January 11, 2005. The pending claims appear in Appendix A.

SUMMARY OF CLAIMED SUBJECT MATTER

The Applicant's invention is directed to solving a problem in the delivery of an active ingredient, such as mesalazine, to the colon for treating inflammatory bowl disease. (p. 2, l. 10-17) The prior art formulations for releasing mesalazine used a coating layer which dissolved at a pH of about 5-6, but the release within the various sections of the colon was very inconsistent. (P. 3, l.28-p.4, l. 3) The prior art formulations thus fail to provide a homogeneous distribution of the active ingredient in the areas of the colon affected by inflammatory bowel disease.

The applicants invention solves this problem by providing a pharmaceutical formulation for a pH dependant multiphasic release of an active ingredient in all the intestinal areas where inflammatory bowel disease occurs (pg. 4, l. 10-17) Each of a plurality of portions of the active ingredient is combined with one of a corresponding plurality of pH dependent soluble polymers

or mixtures of polymers, each of the plurality of polymers or mixture of polymers having a pH solubility beginning at a different pH value. (See example 4, 4.1, 4.2, 4.3).

The active ingredient is preferably provided in three portions in a 1:1:1 ratio, one third of the dose having a coating for release starting at a pH of 6, one third having a coating for release starting at pH 6.5 and a last third having a coating for release starting at pH 7. (P. 6, l. 1-8)

Claim 35 is the only independent claim and this requires a "formulation having at least three coated active ingredient portions, a first portion having a coating soluble starting from a pH of 6, a second portion having a coating soluble starting from a pH of 6.5 and a third portion having a coating soluble starting from a pH of 7".

The separate portions of active ingredient with their different coatings form the pharmaceutical formulation of the invention. It was discovered by the inventor that such a formulation having at least three active ingredient portions released at three different pH values corresponding to each of the different pH solubilities, provides a multiphasic release of the active ingredients for more homogeneous distribution of the active ingredient in different sections of the colon.

Example 2.4 has a three portion mixture, in accordance with claim 1, and had the following dissolution profile:

Table 5

Time	Medium	% dissolution
2nd hour	HCl 0.1N	8.20%
3rd hour	Tampon pH 6.0	31.7%
4th hour	Tampon pH 6.5	58.9%
6th hour	Tampon pH 7.0	94.1%

This illustrates the homogeneous dissolution of the active in three different pH zones, corresponding to the different areas of the colon.

The therapeutic effectiveness of the inventive formulation was confirmed by clinical evaluation, in comparison to two prior art mesalazine formulations known as Asacol® and Claversal®. The procedure is described in Example 13[1]. The following Table 19 shows that the inventive formulation provides more homogeneous tissue concentrations of mesalazine throughout the colon:

Table 19

Product	ILE	ICV	CAE	ASC	HEP	TRA	SPL	DES	SIG	REC	Average
Asacol®	468.1	551.4	503.7	362.2	230.4	313.3	296.4	121.6	115.2	106.4	306.87
Claversal®	171.5	107.4	97.1	116.4	80.3	123.7	104.6	105.1	80.7	90.7	107.75
Formulation of example 6	321.4	380.3	390.8	360.8	290.4	263.6	220.1	180.6	140.3	110.2	265.85

Legend:

ILE = terminal ileum
ICV = cecal ileum valve
CAE = cecum
ASC = ascending colon
HEP = hepatic flexure
TRA = transverse colon
SPL = splenic flexure
DES = descending colon
SIG = sigmoid colon
REC = rectum

1 Example 13 states that the formula of example 2.4 was used, the reference to the formulation of example 6 in the Table being an obvious error.

Using the present invention, a new pH dependant multiphasic formulation for administering an active ingredient homogeneously through various areas of the colon is achieved.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. WHETHER CLAIMS 35 AND 37 – 46 ARE OBVIOUS UNDER 35 U.S.C. § 103(a) OVER HIRAKAWA ET AL U.S. PATENT 5,725,880 IN VIEW OF KHAN ET AL, "A PH-DEPENDANT COLON TARGETED ORAL DELIVERY SYSTEM USING METHACRLYLIC ACID COPOLYMERS I. MANIPULATION OF DRUG RELEASE USING EUDRAGIT® L100-55 AND EUDRAGIT® S100 COMBINATIONS".

ARGUMENT

I. NEITHER REFERENCE TEACHES MULTIPLE PH RELEASE ACTIVE PORTIONS

To establish a prima facie case of obviousness based on a combination of various references, there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant. In re Raynes, 7 F.3d 1037, 1039, 28 U.S.P.Q.2D (BNA) 1630, 1631 (Fed. Cir. 1993); In re Oetiker, 977 F.2d 1443, 1445, 24 U.S.P.Q.2D (BNA) 1443, 1445 (Fed. Cir. 1992). Obviousness can not be established by hindsight combination to produce the claimed invention. In re Gorman, 933 F.2d 982, 986, 18 U.S.P.Q.2D (BNA) 1885, 1888 (Fed. Cir. 1991).

> The genius of invention is often a combination of known elements which in hindsight seems preordained. To prevent hindsight invalidation of patent claims, the law requires some "teaching, suggestion or reason" to combine cited

> references. Gambro Lundia AB v. Baxter Healthcare Corp., 110 F.3d 1573, 1579, 42 U.S.P.Q.2D (BNA) 1378, 1383 (Fed. Cir. 1997). When the art in question is relatively simple, as is the case here, the opportunity to judge by hindsight is particularly tempting. Consequently, the tests of whether to combine references need to be applied rigorously. See In re Dembiczak, 175 F.3d 994, 999, 50 U.S.P.Q.2D (BNA) 1614, 1617 (Fed. Cir. 1999), limited on other grounds by In re Gartside, 203 F.3d 1305, 53 U.S.P.Q.2D (BNA) 1769 (2000) (guarding against falling victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher). McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1351 (Fed. Cir., 2001)

As discussed in Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1143, 227 U.S.P.Q. (BNA) 543, 551 (Fed. Cir. 1985), it is the prior art itself, and not the applicant's achievement, that must establish the obviousness of the combination.

The examiner has failed to consider objectively the references as a whole and failed to consider what each reference would fairly teach or suggest to one of ordinary skill in the art. Rather, the examiner has engaged in a speculative reconstruction of the applicants' invention. Given due consideration, neither reference teaches suggests or even hints at the applicants' invention.

Claim 35 requires a "formulation having at least three coated active ingredient portions, a first portion having a coating soluble starting from a pH of 6, a second portion having a coating soluble starting from a pH of 6.5 and a third portion having a coating soluble starting from a pH of 7".

Hirakawa does not teach or suggest dividing an active ingredient into a plurality of portions, each portion receiving its own coating for initial dissolution at different pH values. Hirakawa provides "a core containing a medicinal active ingredient" and "a press coated layer comprising an enteric polymer, said layer being provided around the core." (col. 2, l. 40-42). The mechanical pressing increases acid resistance. Examples 1-5 all describe a single active

core tablet that is "press-coated", that is, there is only a single active ingredient portion, coated for initial release of the active ingredient at a single pH.

The press coated layer can have multiple layers, or be an admixture of two or more enteric polymers (col. 5, l. 46-58) but even so, there is still only one press coated layer (b) surrounding an active core. The active cannot be released until the press coated layer has been penetrated. This bears no resemblance to the claimed invention, and corresponds to the prior art discussed in the background section of the present application.

Khan also does not teach or suggest a formulation having a plurality of active portions, each coated with a different material for initial dissolution at different pH values.

Khan states: "the main objective of our study was to develop a single coating system for colon targeted delivery of drugs that would allow the dosage form to pass the jejunum (pH 6.1-7.2, residence time 1 h) intact, start disintegrating at the lower small intestine (pH 7.0-7.8, residence time 2 h) and slowly release the drug either at the small intestine or to the colon (pH 6.5, residence time 2 h)...". Similar to Hirakawa, the method involved preparation of a core tablet, with a single coating made up of various ratios of L100-55 and S100 coating polymers. Nowhere in Khan is there any mention of a formulation containing separate active ingredient portions, each coated with a different coating material having a different initial pH solubility.

Generally, a two component coating with various ratios of these two components provides the "single coating" in Khan, similar to Hirakawa disclosing multiple layers or an admixture of enteric coating polymers.

The examiner misread Khan Table 1, a disintegration test. In rejecting the present claims, the examiner stated that "the Khan coated layer disintegrates at different pHs. Specifically, Table 1, page 218, formulation 3:2 at level 13.9 disintegrates at pH of 6.0, 6.5, 6.8 and 7.0."

First, every one of the tested formulations used only a single coating on a single active core, the formulations differing only in the ratios of the coating polymers. This test only showed how long it took to dissolve the coated tablets having different polymer ratios at different pH values, and with different coating weights. The thickest 3:2 formulation disintegrated in 77-83 minutes at a pH of 6.0, 29-31 minutes at pH of 6.5, 24-27 minutes at pH 6.8, 21-25 minutes at pH 7.0. Given this information, the examiners' chosen 3:2 formulation would fail as a delivery system. It would dissolve entirely within "the jejunum (pH 6.1-7.2, residence time 1 h)", violating one of the parameters set out in the article. In any event, such disintegration data on a single coated tablet does not teach or suggest the separation of an active ingredient into discrete coated portions for a multiphasic release, rather it leads one in the opposite direction.

Each formulation of Table 1 has only one pH at which significant dissintegration begins. This can be identified from top to bottom with increasing pH, the last entry for the 0:1 formulation disintegrating at a pH of 7.5. Many of these formulations initially disintegrate at the pH of 6.0, many at 6.5, and fewer at 6.8. It is difficult to imagine how this leads one skilled in the art to the present invention, particularly as what was sought was a formulation that had an initial disintegration pH of 6.8.

As stated on page 219, the most promising formulation was the one that had a ratio of 1:5, which has an initial disintegration at pH 6.8, dissolving slowly at 6.8 but with increased speed at the pH of 7.0 and at 7.5.

The discussion section recommends "a coating formulation" with an L100-55/S100 combination that has about 16.7 % S100, w/w, of the total polymer applied "for colon targeted delivery systems." (p. 222)

One skilled in the art, looking at Hirakawa, a press coated article that relies on the

pressing effect to increase acid resistance, and Khan, which relies on varying the coating polymer ratio to alter the dissolution profile as showing that single coated systems are adequate to provide a sustained release of an active ingredient in the colon. One might be motivated to use the Khan 1:5 polymer ratio for press coating with the Hirakawa system, but there is nothing to teach or suggest the applicants multiphasic formulation of the present invention, comprised of at least three coated active ingredient portions, each coatings providing a different initial solubility for the different active ingredient portions.

II. SUMMARY

"The record must provide a teaching, suggestion, or reason to substitute . . . . The absence of such a suggestion to combine is dispositive in an obviousness determination." Gambro Lundia AB v. Baxter Healthcare Corp., 110 F.3d 1573, 1578-79, 42 U.S.P.Q.2D (BNA) 1378, 1383 (Fed. Cir. 1997).

Neither of the references cited by the examiner teaches or suggests, or even hints that the multiple portion formulation of the invention could or should be used and certainly nothing to suggest the success in the more homogeneous distribution of drug in the colon as shown by the clinical evaluation of the present invention. Thus, the applicants' invention solves a significant problem in the delivery of an active ingredient for the treatment of inflammatory bowel disease, is a significant advance in the art, and patentable over the cited references.

The Examiner has pointed to nothing in the cited references which teaches or suggests the multiple coated portions of the applicants' invention. Consequently, claims 35 and 37-46 are patentable over the art cited by the Examiner.

CONCLUSION

Based on the above remarks, claims 35 and 37-46 are unobvious and reversal of the rejection is respectfully requested.

Dated: July 11, 2005

Respectfully submitted,

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APPENDIX A

35. A pharmaceutical formulation for multiphasic release of an active ingredient for treating inflammatory bowel disease comprising:

a plurality of portions of the active ingredient, the plurality of active ingredient portions being an effective amount sufficient to treat inflammatory bowel disease, each of the plurality of portions having a different coating selected from a corresponding plurality of coatings consisting of different pH dependant soluble polymers or mixture of polymers, the plurality of different coatings soluble in a pH range of from about 6 to about 7, the formulation having at least three coated active ingredient portions, a first portion having a coating soluble starting from a pH of 6, a second portion having a coating soluble starting from a pH of 6.5 and a third portion having a coating soluble starting from a pH of 7, such that each active ingredient portion is released starting at a pH corresponding to the solubility of the coating thereon.

36. (Cancelled)

37. The pharmaceutical formulation according to claim 35 wherein the first portion comprises 10 to 60% of the formulation, the second portion comprises from 10 to 60% of the formulation and the third portion comprises from 10 to 60% of the formulation.

38. The pharmaceutical formulation of claim 35 wherein the active ingredient in mesalazine.

39. The pharmaceutical formulation according to claim 35 wherein the active ingredient is selected from the group consisting of steroids, antibiotic, anti-inflammatories and combinations thereof.

40. The pharmaceutical formulation according to claim 35 wherein the plurality of active ingredient portions are in a form selected from the group consisting of microtablets, tablets, granules, microgranules, pellets and combinations thereof.

41. The pharmaceutical formulation according to claim 35 wherein the formulation is in a form of a multilayer tablet.

42. The pharmaceutical formulation according to claim 35 wherein at least one coated active ingredient portion is in a unitary form selected from the group consisting of a tablet, a layer and a microtablet, and wherein the unitary form further comprises a second coating thereon, the second coating containing from 5-35% of the same coating as the at least one coated active ingredient portion, from 0 to 10% of a fatty acid having from 12-20 carbon atoms and from 0 to 10% of a pharmaceutically acceptable plasticizer.

43. The pharmaceutical formulation according to claim 35 wherein the at least one coating is soluble starting at a pH of 6, and is selected from the group consisting of poly(methacrylic-co-methyl methacrylate), 1:1, 135,000MW, cellulose acetatephtalate, hydroxypropylmethylcellulosephtalate, hydroxypropylmethylcelluloseacetatesuccinate type L and mixtures thereof.

44. The pharmaceutical formulation according to claim 35 wherein the at least one coating is soluble starting at a pH of 6.5 and is selected from the group consisting of poly(methacrylic acid-co-methyl methacrylate), 1:1, 135,000 MW, Hydroxypropylmethylcellulosephtalate, Hydroxypropylmethylcelluloseacetatesuccinate type L in a mixture 1:1 with poly(methacrylic acid-co- methylmethacralate), 1:2, 135,000 MW, and mixtures thereof.

45. The pharmaceutical formulation according to claim 35 wherein the at least one coating is soluble starting at a pH of 7 and is selected from the group consisting of poly(methacrylic acid-co-methacrylate), 1:2, 135,000 MW, poly(methylacrylate-co-methyl methacrylate-co-trimethacrylic acid), 7:3:1, 400,000 MW, or Hydroxypropylmethylcellulosephtalate type M, and mixtures thereof.

46. The pharmaceutical formulation according to claim 35 wherein the first coated portion comprises 30-35% of the formulation, the second coated portion comprises 30 to 35% of the formulation and the third coated portion comprises 30 to 35% of the formulation.